The clinical importance of parathyroid atypia: Is long-term surveillance necessary?

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Background. *The uncommon diagnosis of atypical parathyroid adenoma (APA) creates a clinical conundrum for surveillance. We evaluated a large series of APA to determine long-term outcomes.*
Methods. *Prospectively collected data were retrieved for patients with a diagnosis of histologic APA defined by presence of ≥2 criteria: clinical/intraoperative adherence, fibrotic bands, trabecular growth, or mitotic rate of >1/10 per high-power field without indisputable signs of malignancy. Follow-up was at 2 weeks, 6 months, and yearly thereafter.*
Results. *From 1970 to 2014, 51 patients (1.2%) with primary hyperparathyroidism had a diagnosed APA. Mean age was 56 years (range, 19–83), and 61% were women. Intraoperatively, 11 of 51 glands (22%) were adherent, requiring concurrent thyroid lobectomy. Common microscopic findings were fibrosis (78%), trabecular growth (37%), and increased mitotic count (24%); the mean APA weight was 3.14 g (range, 167 mg–38 g). Loss of heterozygosity occurred in 25 of 38 tested patients (66%) at the* p21 *locus in 9 cases, at* CDC73 *and* PTEN *in 6, and at* RB1 *in 4 cases, with mean fractional allelic loss of 24% (range, 6–79). With mean follow-up of 5 years (range, 0.5–18), no patient has developed recurrence.*
Conclusion. *Over a mean follow-up of 5 years, we observed no recurrences after APA resection. Molecular features had no discernable impact, indicating that long-term follow-up may be unnecessary. (Surgery 2015;158:929-36.)*

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Primary hyperparathyroidism is a common endocrine disorder, but parathyroid carcinoma is quite rare. Seen in <1% of cases of primary hyperparathyroidism in the United States, parathyroid carcinoma affects men and women equally, and its management and outcome are variable.[1-3] Intraoperatively, parathyroid carcinoma has a characteristic appearance, including adherence to adjacent structures, being densely firm, and having a gray/white consistency. Despite their rarity, parathyroid carcinoma has been well-characterized in the literature, and is diagnosed histologically by the presence of vascular, perineural invasion of soft tissue or surrounding structures, or in the setting of documented metastatic disease.

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A subset of parathyroid neoplasms exist that do not quite fulfill the criteria for parathyroid carcinoma, yet have features that are either clinically or histologically more worrisome than those of the typical adenoma. This type of tumor, designated as atypical parathyroid adenoma (APA), often has a similar appearance to parathyroid carcinoma, and discerning parathyroid carcinoma from APA grossly is not often feasible.[4] APA does not have a standardized or universally accepted definition; diagnosis is based on the presence of criteria that are worrisome but not definitive for malignancy, including fibrosis, trabecular growth, increased mitotic rate, and the absence of clear histologic signs of carcinoma.[5,6] Testing for loss of heterozygosity (LOH) has aided in the diagnosis of parathyroid carcinoma, particularly when the histologic features and clinical findings are discordant, but its utility for APA is unclear.[7-9] Further, the long-term clinical sequelae of a histologic diagnosis of APA are not well defined. The goal of our study was to delineate long-term outcomes after removal of APA to guide clinical management and surveillance.

METHODS

With institutional approval (#PRO08090450 and PRO11020368), a prospectively collected clinical database was queried for patients with single gland disease diagnosed as APA on final surgical pathology from May 1973 to August 2014. All APA cases were reviewed for this study by 1 of 3 head and neck–trained pathologists. APA was defined by the presence of ≥2 of the following characteristics: clinical/intraoperative adherence, bands of fibrosis, pronounced trabecular growth, and mitotic rates of >1/10 high-power fields (hpfs) [5–6]. APA also lacked any of the indisputable criteria for malignancy, including invasion of vascular, perineural, soft tissue, or surrounding structures (including thyroid, recurrent laryngeal nerve, trachea, esophagus) or documented metastatic disease.[1,2,10-12] Follow-up was performed within 2 weeks after operation, at 6 months, and then yearly, and included routine serum calcium and parathyroid hormone (PTH) measurements. Annual surveillance imaging also consisted of cervical ultrasonography and/or neck CT. Demographic, clinical, biochemical, pathologic, and outcome data were retrieved for each case of APA.

The clinical and pathologic data were also compared with 2 separate, previously described cohorts of patients with primary hyperparathyroidism who underwent parathyroidectomy during the same time period. The benign adenoma cohort included 814 patients cured after resection of a single adenoma during parathyroid exploration for sporadic primary hyperparathyroidism.[13] The cohort with parathyroid carcinoma included 41 patients, 19 of whom have been described previously.[9] The clinical and histopathologic data as well as LOH patterns of adherent and nonadherent APAs were also compared. Patients in any of the study cohorts with anatomic, multiglandular disease defined by intraoperative findings and normocalcemia at the 6-month follow-up.

Testing for LOH is performed at our institution for APA and parathyroid carcinoma as part of clinical care. In our previous study of parathyroid carcinoma, cases from the era before use of LOH were reviewed again and LOH performed.[9] LOH for 20 microsatellite markers corresponding to a panel of 12 loci of tumor suppressor genes was determined as described previously.[7-9] Fractional allelic loss was calculated as the percentage of loci with LOH divided by number of informative loci.[7]

Statistical analysis (SPSS software, IBM) was performed using 1-way analysis of variance for continuous data and the Chi-square test for categorical data when comparing >2 groups and Student's t and Fisher's exact tests were used when comparing 2 subsets.

RESULTS

Patients. During the study period, 4,390 patients underwent parathyroid exploration for biochemically confirmed sporadic primary hyperparathyroidism; 51 (1.2%) were diagnosed with an APA. None of the patients with APA had preoperative fine needle aspiration biopsy of the parathyroid gland obtained as part of diagnostic evaluation. Of the APA patients, 61% were women compared with 81% of benign adenoma patients and 59% of parathyroid carcinoma patients ($P < .01$). The mean age was 56 years (range. 19–83) for those with APA, which did not differ from those with benign adenoma (mean, 60; range, 19–94) and those with parathyroid carcinoma (mean, 57; range, 25–77; $P < .07$). The mean preoperative serum calcium concentrations were different among the cohorts ($P < .01$). Post hoc analysis showed that calcium levels were significantly less in patients with benign adenoma (11.4 mg/dL; range, 9.1–18.9) compared with those with APA (11.8 mg/dL; range, 10.8–15; $P = .04$) and parathyroid carcinoma (12.4 mg/dL; range, 10.3–19.6; $P < .01$). There was no difference in mean preoperative high calcium level between APA and parathyroid carcinoma. Mean preoperative PTH levels also differed by pathologic categories ($P < .01$). PTH levels were significantly less in patients with benign adenoma (157 pg/mL; range, 54–9,098) compared with parathyroid carcinoma (368 pg/mL; range, 68–2,023; $P < .01$). PTH levels were similar between patients with benign adenoma and APA (172 pg/mL; range, 59–358; $P = .9$) and APA and parathyroid carcinoma ($P = .1$). The Table presents patient demographic and clinical data including gland weight.

Anatomic and pathologic findings. All 51 APA patients had single gland disease with a predominance of atypical superior glands (67%). One patient with APA had a palpable neck mass that weighed 10,902 mg and was adherent to the thyroid gland; this patient's Ca and PTH levels were 12.7 mg/dL and 171 pg/mL, respectively. In 11 of 51 patients (22%), the parathyroid gland was adherent to an adjacent structure, and in only 1 of these patients (9%) were the preoperative imaging results suspicious for adherence or possible parathyroid carcinoma. In these 11 patients, en bloc